Colorectal Cancer Screening and Surveillance
Residual Risk after Colonoscopy: Right vs Left Colon

- Brenner 2011
- Singh, G 2007
- Singh, H 2010
- Baxter, 2009

Legend:
- Left-sided
- Right-sided
# Colorectal Cancer Molecular Basis

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Frequency</th>
<th>Genes</th>
<th>MSI</th>
<th>Precursor</th>
<th>Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN</td>
<td>70-75%</td>
<td>APC, k-ras, p53</td>
<td>No</td>
<td>Adenoma</td>
<td>Slow</td>
</tr>
<tr>
<td>Lynch</td>
<td>3%</td>
<td>MLH1, MSH2, MLH6, PMS2</td>
<td>Yes</td>
<td>Adenoma</td>
<td>Fast</td>
</tr>
<tr>
<td>CIMP</td>
<td>20-30%</td>
<td>BRAF</td>
<td>Sometimes</td>
<td>Serrated</td>
<td>Can be fast</td>
</tr>
</tbody>
</table>
Two Classes of Precancerous Lesions in the Colorectum

• Conventional adenomas
  • Dysplasia grade (low vs high)
  • Villousity (tubular vs tubulovillous vs villous)
• Serrated class
  • Sessile serrated polyp/adenoma
  • Traditional serrated adenoma
Expanded Terminology of Serrated Lesions (WHO)

• Hyperplastic polyp (HP)
  • Goblet cell HP
  • Microvesicular HP
  • Mucin Poor HP
• Sessile serrated adenoma/polyp (SSA/P)
  • With cytological dysplasia
  • Without cytological dysplasia
• Traditional serrated adenoma (TSA)
Pathologic Differentiation of SSA/P from HP

MVHP

SSA/P
Agreement for Pathologic Interpretation of SSA/P vs HP

  - SSA commonly read as HP
  - TSA commonly read as TVA
- Khalid et al World J Gastroenterol 2009
  - 30-80% of proximal HPs in 2001 read as SSP by experts; kappas 0.14-0.38
SSA/P Without and With Cytological Dysplasia

SSA/P without dysplasia

SSA/P with dysplasia
The Serrated Pathway

Hyperplastic polyp
  ↓  probaby slow
Sessile serrated adenoma/polyp
  ↓  sometimes fast
SSA/P with cytologic dysplasia
  ↓  CIMP colon cancer
2416 SSA/Ps

mean age

- SSA/P: 61y
- SSA/P with LGD: 66y
- SSA/P with HGD: 72y
- SSA/P with cancer: 76y

• Lash J Clin Pathol 2010;63:681-6
Histology of Colon Polyps – Reliable or Not?

**Yes**
- Serrated vs conventional adenoma
- Cancer or no cancer

**Not very**
- Tubular vs tubulovillous
- HGD vs LGD
- Tumor differentiation
- SSA/P vs HP
# Features of Major Categories of Serrated Lesions

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Prevalence</th>
<th>Shape</th>
<th>Size</th>
<th>Distribution</th>
<th>Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>Very common</td>
<td>Sessile/flat</td>
<td>small</td>
<td>Mostly distal</td>
<td>Very low</td>
</tr>
<tr>
<td>Sessile serrated adenoma/Polyp</td>
<td>Common</td>
<td>Sessile/flat</td>
<td>Big</td>
<td>80% proximal</td>
<td>Significant</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td>Rare</td>
<td>Sessile/pedunculated</td>
<td>Big</td>
<td>Mostly distal</td>
<td>Significant</td>
</tr>
</tbody>
</table>
# Spectrum of Pre-cancerous Lesions in the Colorectum

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Paris shape</th>
<th>Distribution</th>
<th>Prevalence</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional adenomatous polyps</td>
<td>1p</td>
<td>Left</td>
<td>Low</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td></td>
<td>1s</td>
<td>Throughout</td>
<td>Common</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td>Flat adenomas (lesions)</td>
<td>2a</td>
<td>Greater to right</td>
<td>Common</td>
<td>Mostly LGD</td>
</tr>
<tr>
<td>Depressed adenomas (lesions)</td>
<td>2c</td>
<td>Greater to right</td>
<td>rare</td>
<td>↑↑ HGD and invasive cancer</td>
</tr>
<tr>
<td></td>
<td>2a + 2c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2c + 2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessile serrated adenoma (polyp)</td>
<td>1s or 2a</td>
<td>Greater to right</td>
<td>Common</td>
<td>Distinction from HP may not be reliable</td>
</tr>
<tr>
<td>TSA</td>
<td>1s or 1p</td>
<td>Left colon</td>
<td>rare</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
Pale, Sessile, Indistinct Edges, Lacy Blood Vessels
Serrated Lesion with Mucus Cap
SSP with Cytological Dysplasia
Changes in Epidemiology of Colorectal Cancer

• Major incidence declines since 1985
  • Accelerated declines in persons over age 50 beginning in 2000
• Incidence rates are rising in persons under age 50
  • % of all cases under age 50 has about doubled (7% → 15%)
  • USPSTF analysis suggested age 45 was most cost-effective age to begin screening
• Aggressive evaluation of symptomatic patients recommended
USPSTF Screening Recommendations

• CRC screening has grade A recommendation
• No ranking of tests
• Offer screening from ages 45-75 years
  • Stop at 85
  • Individualize between age 75 and 85
American Cancer Society Recommendations

• Start screening at age 45
  • “qualified recommendation”
  • Based on modeling on new data on incidence rates
• No ranking of tests
Approaches to Screening

• Organized (programmatic)
  • Usually based on FIT

• Opportunistic (office-based)
  • Usually based on colonoscopy
Ways to Offer Screening

• Multiple options
  • Offering more than 2 options does not increase total adherence

• Sequential screening
  • May maximize adherence rates and maximize use of the most effective test

• Risk stratified screening
  • Offer FIT to younger persons especially women; colonoscopy to older persons
Multi-Society Task Force (ASGE, ACG and AGA)

• Begin screening at age 45
• Tests are ranked to make process of offering screening more practical:
  • Effectiveness
  • Cost-effectiveness
  • Evidence of uptake
  • Practical features
What Tests to Offer: MSTF Recommendations

• Tier 1
  • Colonoscopy every 10 years
  • Annual FIT

• Tier 2
  • Flex sig every 5-10 years
  • CTC every 5 years
  • Cologuard every 3 years

• Tier 3
  • Capsule colonoscopy

• Don’t use
  • Septin 9 plasma assay
Colonoscopy

• Provides longest interval of protection
• Gold standard and unmatched for cancer detection and polyp detection
• The only strategy that provides cancer prevention through polyp removal
Fecal Immunochemical Test (FIT)

- Stool test that checks for hemoglobin
- Assumes cancers will bleed
- Once a year
- Requires stool sample be obtained
FIT Testing

• Threshold for detection of hemoglobin
  • 20 μg/gram feces

• Advantages
  • Done at home
  • Low cost - $22
  • Better adherence in organized settings (Kaiser)

• If threshold for hemoglobin 10 μg/gram feces
  • Sensitivity for cancer: 91%
FIT Testing – Take Home Points

• Low cost
• Easy to use
• Good (but not great) sensitivity for CRC
  • Much improved if decreased for hemoglobin threshold
• Colonoscopy is needed if test is positive
• Only prevents cancer when it results in colonoscopy
FIT-Fecal DNA Test

• Currently available: Cologuard®
• Contains a FIT
• DNA assays:
  • K-ras
  • B-actin
  • NDRG4 and BMP3 methylation
# Fecal DNA – The “Deep C” Trial - Imperiale et al NEJM 2014

<table>
<thead>
<tr>
<th>Finding</th>
<th>N</th>
<th>Parameter</th>
<th>Fecal DNA</th>
<th>FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CRC</td>
<td>64</td>
<td>Sensitivity</td>
<td>92.2%</td>
<td>73.4%</td>
</tr>
<tr>
<td>CRC I-III</td>
<td>60</td>
<td>Sensitivity</td>
<td>93.3%</td>
<td>73.3%</td>
</tr>
<tr>
<td>All Adv. Ad.</td>
<td>752</td>
<td>Sensitivity</td>
<td>42.4%</td>
<td>23.8%</td>
</tr>
<tr>
<td>AA ≥ 2 cm</td>
<td>116</td>
<td>Sensitivity</td>
<td>65.5%</td>
<td>43.1%</td>
</tr>
<tr>
<td>SSP ≥ 1 cm</td>
<td></td>
<td>Sensitivity</td>
<td>42.4%</td>
<td>5.1%</td>
</tr>
<tr>
<td>All else</td>
<td>9118</td>
<td>Specificity</td>
<td>86.6%</td>
<td>94.9%</td>
</tr>
<tr>
<td>No adenoma</td>
<td>6237</td>
<td>Specificity</td>
<td>89.8%</td>
<td>96.4%</td>
</tr>
<tr>
<td>Advantages</td>
<td>Limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninvasive</td>
<td>Less sensitive for cancer than high-quality colonoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (92%) sensitivity for cancer</td>
<td>Less sensitive for adenomas and serrated lesions than colonoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended at 3-year intervals (compared to 1 year for FIT)</td>
<td>High (12%) false-positive rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>False-positive rate increases with patient age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expensive ($500) compared to FIT ($22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most of the sensitivity derives from the FIT, which itself is inexpensive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dominated by FIT in cost models: FIT is more effective and cost-effective than the FIT-fecal DNA test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No evidence to support use outside of screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basis for positive results (FIT or DNA stool tests, or both) is not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colonoscopy for a positive FIT-fecal DNA test is considered part of the continuum of care for colon cancer screening. There is no out-of-pocket cost for the colonoscopy.

Rex, D. PRACTICAL ADVICE FOR COLORECTAL CANCER SCREENING. GI & Hepatology News 2019
What Tests to Offer MSTF Recommendations

• Tier 1
  • Colonoscopy every 10 years
  • Annual FIT

• Tier 2
  • Flex sig every 5-10 years
  • CTC every 5 years
  • FIT-Fecal DNA Test (Cologuard®) every 3 years

• Tier 3
  • Capsule colonoscopy

• Don’t use
  • Septin 9 plasma assay
# Colonoscopy Prevent CRC and CRC Mortality

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Design</th>
<th>Primary endpoint</th>
<th>Residual risk</th>
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</thead>
<tbody>
<tr>
<td>Kahi 2009</td>
<td>U.S.</td>
<td>Cohort</td>
<td>Incidence</td>
<td>0.33</td>
</tr>
<tr>
<td>Baxter 2009</td>
<td>Canada</td>
<td>Case-control</td>
<td>Mortality</td>
<td>0.63</td>
</tr>
<tr>
<td>Mulder 2010</td>
<td>Netherlands</td>
<td>Case-control</td>
<td>Incidence</td>
<td>0.56</td>
</tr>
<tr>
<td>Singh 2010</td>
<td>Canada</td>
<td>Cohort</td>
<td>Mortality</td>
<td>0.71</td>
</tr>
<tr>
<td>Brenner 2011</td>
<td>Germany</td>
<td>Case-control</td>
<td>Incidence</td>
<td>0.23</td>
</tr>
<tr>
<td>Baxter 2012</td>
<td>U.S.</td>
<td>Case-control</td>
<td>Mortality</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Colonoscopy Prevents Right Sided Colon Cancer and Cancer Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Primary outcome</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brenner</td>
<td>2011</td>
<td>Germany</td>
<td>Case-control</td>
<td>Incidence</td>
<td>0.58</td>
</tr>
<tr>
<td>Baxter</td>
<td>2012</td>
<td>U.S.</td>
<td>Case-control</td>
<td>Mortality</td>
<td>0.44</td>
</tr>
</tbody>
</table>
## Colonoscopy Protection May Be > 20 Years

<table>
<thead>
<tr>
<th>Interval</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 years</td>
<td>0.14</td>
<td>0.10-0.20</td>
</tr>
<tr>
<td>3-4 years</td>
<td>0.12</td>
<td>0.08-0.19</td>
</tr>
<tr>
<td>5-9 years</td>
<td>0.26</td>
<td>0.18-0.39</td>
</tr>
<tr>
<td>10-19 years</td>
<td>0.28</td>
<td>0.17-0.45</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>0.40</td>
<td>0.24-0.66</td>
</tr>
</tbody>
</table>
Colonoscopy – is Operator Dependent
Variable Detection of Adenomas Among GI Docs During Colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Number of doctors</th>
<th>Lowest ADR</th>
<th>Highest ADR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barclay Illinois 2006</td>
<td>12</td>
<td>9.4%</td>
<td>32.7%</td>
<td>3.5</td>
</tr>
<tr>
<td>Chen Indiana 2007</td>
<td>9</td>
<td>15.5%</td>
<td>41.1%</td>
<td>2.7</td>
</tr>
<tr>
<td>Imperiale Indiana 2009</td>
<td>25</td>
<td>7%</td>
<td>44%</td>
<td>6.3</td>
</tr>
<tr>
<td>Shaukat Minnesota 2009</td>
<td>51</td>
<td>10%</td>
<td>39%</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Variable Detection of Proximal Serrated Lesions (GI Docs) During Colonoscopy

<table>
<thead>
<tr>
<th></th>
<th>Number of doctors</th>
<th>Lowest proximal colon serrated lesion detection rate</th>
<th>Highest proximal colon serrated lesion detection rate</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hetzel Boston</td>
<td>13</td>
<td>1.1%</td>
<td>7.6%</td>
<td>6.9</td>
</tr>
<tr>
<td>Kahi Indiana</td>
<td>15</td>
<td>1%</td>
<td>18%</td>
<td>18</td>
</tr>
</tbody>
</table>
## Operator Dependence – Cancer Prevention

Kaminski et al NEJM2010;362:1795-803

<table>
<thead>
<tr>
<th>Adenoma detection rate (ADR)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11%</td>
<td>10.94</td>
</tr>
<tr>
<td>11.0 14.9%</td>
<td>10.75</td>
</tr>
<tr>
<td>15.0-19.9%</td>
<td>12.50</td>
</tr>
</tbody>
</table>
California Kaiser Study Validates the ADR

• > 700 interval cancers
• 3% reduction in the risk of interval cancer and a 5% reduction in mortality for each 1% increase in the ADR
  • Corley et al NEJM 2014; 370:1298-306
How Do I Get a Good Colonoscopy?

- Split-dose the preparation
- Ask your doctor for their ADR
  - Rex et al GIE;2017;86:18-33
Modifications to Screening Recs

• Start earlier if African-American (age 45)
• Family history
  • Always consider Lynch
  • Count FDRs
  • Consider age (60 year cut-off)
  • If ≥ 2 FDRs or 1 FDR < 60 then start at 40 or 10 years before the age at diagnosis of the youngest affected relative
    • Use colonoscopy at 5 year intervals
Post-Polypectomy Surveillance
Risk Stratification - Adenomas

- Low risk adenomas
  - 1 or 2 tubular adenomas < 10 mm in size: 7-10 years
  - 3 or 4 tubular adenomas < 10 mm in size: 3-5 years

- High risk adenomas
  - Any adenoma ≥ 10 mm: 3 years
  - Any adenoma with villous elements or HGD: 3 years
  - 5-10 adenomas: 3 years
  - > 10 adenomas: 1 year
Risk Stratification - Serrated Lesions

- ≤ 20 HPs in rectum or sigmoid colon < 10 mm: 10 years
- ≤20 HPs proximal to sigmoid colon: 10 mm: 10 years
- 1-2 SSPs < 10 mm: 5-10 years
- 3-4 SSPs < 10 mm: 3-5 years
- 5-10 SSPs < 10 mm: 3 years
- SSP ≥ 10 mm: 3 years
- SSP with dysplasia: 3 years
- HP ≥ 10 mm: 3-5 years
- TSA: 3 years
Summary

• Pre-cancerous lesions: two main types that differ in appearance, amount of bleeding, colon location
• PCPs should encourage screening
• Screening: Colonoscopy q 10 or annual FIT
• Understand FIT-Fecal DNA
• Colonoscopists need to measure quality